outcomes using the following independent variables: 1) sex; 2) sex and age; 3) sex, age and pre-surgery score of the outcome; and, 4) the latter model plus BMI, education level, low back pain (LBP), depression, number of comorbidities, and symptomatic joint count. P values of ≤ 0.05 were considered significant. As change between 6 and 12 months surgery is known to be much less relative to baseline to 6 months, we conducted analyses at 12 months as a validation of the 6 month results.

Results: The sample included 323 females and 171 males. Females had worse pain and function scores at baseline compared to males (pain: 39.0 ± 16.5 in females versus 44.9 ± 16.4 in males, p=0.002; function: 47.7 ± 18.6 in females versus 55.0 ± 17.5 in males, p<0.0001). As well, females had worse pain and function at follow-up (72.2 ± 18.4 vs. 76.1 ± 17.7, p=0.03; 75.2 ± 17.5 vs 80.5 ± 17.1, p=0.003, respectively). Females also had worse pre-surgery depression scores (5.6 ± 3.6 vs 4.7 ± 3.2, p=0.006), higher rates of obesity (BMI ≥30: 54.2 vs. 36.3%, p=0.0002), and higher symptomatic joint count (≥4: 61.3 vs. 44.4%, p=0.0004). Initially, regression findings suggested that females had worse outcomes for pain (p=0.04) and function (p=0.007) compared to males. However, this effect was lost once baseline pain/functional status were also considered. In the final model, worse outcomes were predicted by pre-surgery pain/functional status, as well as depression, LBP and comorbidity count. The results at 12 months were consistent with those at 6 months.

Conclusions: Women appear to have worse outcomes following TKR in part as a function of their greater pain and more limited function pre-surgery. However, depression and comorbidity, for which women have worse status pre-surgery, further contribute to worse outcomes. These finding suggest that women potentially could achieve comparable outcomes to men if surgery were performed before their symptoms and disability became so severe. This could, in addition, limit the effect of mood or, alternately, interventions to address mood could positively influence outcomes.

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IDENTIFICATION OF SEROLOGICAL PROFILES ASSOCIATED WITH TOTAL JOINT REPLACEMENT IN OSTEOARTHRITIS PATIENTS

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Purpose: 1. To identify patients who will progress to requiring total joint replacement (TJR) amongst a population with moderate-to severe-osteoarthritis (OA) by measuring tissue specific biomarkers in serum thus establishing a panel of prognostic biomarkers that may provide molecular insight into the mechanism and pathology of the progression of OA. 2. Investigate the effect of NSAIDs on the predictive and diagnostic serum profile.

Methods: OA patients were randomly selected from clinical trials investigating the anti-NGF therapeutic antibody tanezumab. Serum samples from 240 patients who underwent a TJR (cases) and from 440 control OA patients who did not undergo TJR were used. Control group consisted of ~2 patients per case matched on: age (<65 or ≥ 65 years), Kellgren-Lawrence (K-L) grade, gender, BMI category (<30 or ≥30 kg/m^2), OA severity (severe if both WOMAC Pain and Physical function subscale scores were ≥7 and the Patient Global Assessment score was ≥4 (i.e. Poor or Very Poor), otherwise baseline OA severity was classified as not severe). On the average, the OA population was 62 years old, 80% K-L grade ≥3, females (68%), BMI ~31 kg/m^2, WOMAC pain score of 7. Serum samples were analyzed for bone (Total Osteocalcin, CTX-I, DKK1, SOST), cartilage (C2M, COMP, PIIANP), connective tissue (PINP, ICTP, C1M), synovial tissue (C3M), protease burden (MMP-9) as well as inflammation markers (IL6, hsCRP, VEGF). Classification and Regression Tree analysis was used to identify biomarker phenotypes.

Results: For NSAID and non-NSAID users separately, biomarker phenotypes were identified at baseline for patients predisposed for TJR. At baseline, a biomarker combination for patients who used NSAIDs before start of tanezumab clinical trials identified 96% of patients who underwent a TJR and 61% of the patients who did not undergo a TJR. Identification of these biomarker phenotypes lowers the odds of a TJR by 14-fold as compared to not having knowledge of the biomarkers. For patients who did not use NSAIDs, 83% of patients who had a TJR and 63% of the patients who did not undergo a TJR, were identified which lowers the odds of a TJR by 3.6-fold. For patients who used NSAIDs continuously, 84% of patients who had a TJR and 77% of the patients who did not have a TJR, were identified which lowers the odds of a TJR by 4.7-fold.

Conclusions: Serological biomarker profiles for predicting TJR were identified irrespective of NSAID use and may assist in identifying those patients whom will need a TJR. The profiles also suggest that NSAID use increases the importance of the role of bone metabolism in TJR pathology. The results need validation on other cohorts, and may finally provide value to patients and payers in selecting the most optimal treatment strategy for moderate-to-severe OA patients.

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MALES ARE AT INCREASED RISK FOR SURGICAL COMPLICATIONS FOLLOWING TOTAL JOINT ARTHOPLASTY

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Purpose: The burden of osteoarthritis of the hip and knee is higher in females than in males. Despite this, there remains a gender disparity in the recommendation and uptake of total joint arthroplasty (TJA), with males being more likely to be offered surgery. This may result from a perception that females have a higher rate of complications, including: acute myocardial infarction (AMI), venous thrombo-embolism (VTE), infection, dislocation, early revision, and death. To date, few studies have examined if differences by sex persist in the rates of complications following TJA of the hip (THA) or knee (TKA).

Methods: We defined a cohort of patients who received their first primary elective THA or TKA between 2002-2009 utilizing administrative databases from Ontario, Canada. We excluded those who received a primary or revision arthroplasty of the hip or knee prior to April 1, 2002, those whose first procedure was non-elective (e.g. for cancer, fracture, or injury), or those with a history of hip dysplasia. We compared baseline characteristics and rates of complications following the index TJA for male and female recipients. Cox proportional hazards were used to determine the relationship between sex and the occurrence of specific complications (within 90d: VTE, AMI, mortality; within 2y: dislocation, infection, and revision), defined using validated algorithms, controlling for potential confounders (including income quintile, rurality, and provider volume) and for clustering by surgeons.

Results: Between April 1, 2002 and March 31, 2009, there were 97,445 patients who received their first TJA (males: 41,023 - 42%; females: 56,422 - 58%). Compared with female TJA recipients, males were more likely to have received a THA (43% versus 36%, p<0.001), more likely to come from a rural area (20% versus 15%, p<0.001), and had greater comorbidity (Charlson score of 2+: 5.5% vs 3.5%, p<0.001). Controlling for these differences, and other potential confounders, male TJA recipients were more likely to experience an infection (adjusted HR 1.41, 95%CI 1.24-1.61, p<0.0001), early revision (adjusted HR 1.24, 95%CI 1.10-1.40, p=0.0006), or death (adjusted HR 1.26, 95%CI 1.03-1.55, p=0.03). They were similarly likely to experience all other complications: dislocation (adjusted HR 0.94, 95%CI 0.79-1.12, p=0.48), AMI (adjusted HR 1.05, 95% CI 0.93-1.19, p=0.41), and VTE (adjusted HR 0.99, 95%CI 0.88-1.12, p=0.95).

Conclusions: In a population cohort undergoing their first primary TJA, male recipients were at increased risk for early revision, infection and death relative to female recipients.

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BMP2 REQUIRES TGF-BETA TO INDUCE OSTEOPHYTES DURING EXPERIMENTAL OA

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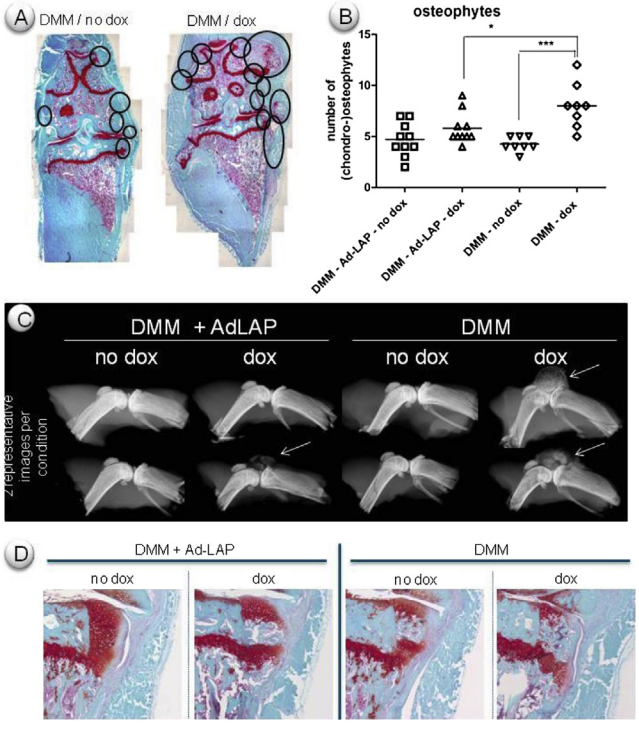
Purpose: Osteophyte formation is one of the hallmarks of osteoarthritis (OA). We have shown that either overexpression of TGF-beta or BMP2 can induce osteophytes in murine knee joints. However, comparing osteophytes induced by experimental OA, TGF-beta or BMP2 showed us that TGF-beta-induced osteophytes rather than BMP2-induced osteophytes more closely resemble those observed in experimental OA. TGF-beta-induced osteophytes develop mainly from

periosteum whereas BMP2-induced osteophytes originated from cells with a more advanced chondrocyte-like phenotype as can found in the growth plate. We additionally demonstrated that in mesenchymal stem cells TGF-beta could induce chondrogenesis when BMP activity was inhibited but not vice versa. This suggested that BMP2 requires an alternative trigger, like TGF-beta, to induce the initiation of chondrogenesis. We wanted to know whether this observation could be extrapolated to osteophyte formation during experimental OA: Can BMP2 induce osteophyte formation in experimental OA when TGF-beta activity is blocked.

Methods: We made a unique transgenic mouse which expresses BMP2 under control of the Col2a1 promoter but only when exposed to doxycycline (Col2a1-rtTA-BMP2). As a result, chondrocytes start to produce BMP2 when this unique transgenic mouse is exposed to doxycycline. We exposed these mice to doxycycline in food up to 8 weeks to investigate osteophyte formation in knee joints using histology. In addition, we induced osteoarthritis by destabilization of the medial meniscus (DMM-model), which amongst others results in osteophyte formation, and investigated whether BMP2 augmented osteophyte formation. Moreover, to investigate whether TGF-beta was required for BMP2-related osteophyte formation we combined the DMM-model with intra-articular injection of an adenovirus overexpressing the specific TGF-beta inhibitor LAP with our without doxycycline to overexpress BMP2. Murine knee joints were isolated 4 weeks after DMM exposure for histology to investigate effects on osteophyte formation.

Results: Four out of 10 dox-treated Col2a1-rtTA-BMP2 mice had more osteophytes than controls, but dox versus non-dox treated groups were not significantly different. When OA was induced, clearly osteophytes developed with an average of 4.25 osteophytes per knee joint. However, when these mice were treated with dox, thus inducing chondrocyte-specific BMP2 expression in addition to OA, we found a significant increase in the number of osteophytes (8.0) compared to DMM non-dox (Figure A, B). These "new" osteophytes were much larger than regular DMM-induced osteophytes (Figure A,C). The lack of osteophytes when treated with dox alone compared to DMM with dox implied that the DMM treatment provided a trigger crucial for BMP2 to be able to aggravate osteophyte formation. To investigate whether TGF-beta was that trigger we inhibited TGF-beta inhibition by i.a. injection of Ad-LAP one day after DMM-induction. This showed that without TGF-beta, BMP2 was no longer capable of augmenting the number of osteophytes during DMM as there were no significant differences in osteophyte number comparing DMM-Ad-LAP treated animals with or without dox (Figure B,C). When focusing on the osteophytes that regularly develop during DMM originating from the periost on the medial side of the joint,we found an additional striking finding: the inhibition of TGF-beta early during OA significantly reduced the speed of osteophyte formation which therefore were still in a chondrophyte at the moment of sacrifice of the mice. This effect was completely abolished by the additional presence of BMP2 which restored the osteophyte maturation from chondrophyte to osteophyte.



Conclusions: Our data show that BMP2 is capable of inducing osteophyte formation, but is dependent on an additional prior trigger to achieve this, as present in OA. In OA conditions, BMP2 can severely aggravate osteophyte formation, both in number and size. However, when TGF-beta is blocked BMP2 is no longer capable of aggravating osteophyte formation during DMM. Strikingly, early inhibition of TGF-beta during OA impaired the speed of osteophyte formation, which could be compensated by the presence of BMP2. Our data show for the first time that BMP2 is dependent on TGF-beta to induce de novo osteophyte formation. This provides novel insight into the mechanism behind osteophyte formation and provides clues for future therapeutic application for osteophyte formation in OA.

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INHIBITION OF TGF-β1 ATTENUATES ARTICULAR CARTILAGE DEGENERATION IN MATURE KNEE JOINTS OF MOUSE MODELS OF OSTEOARTHRITIS

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Background: The goal of this study is to understand role of transforming growth factor beta 1 (TGF-β1) in development of osteoarthritis (OA). Results from studies indicate that the genetic inactivation of Smad-3, or the disruption of the interaction of Tgf-β1 with its receptor Tgf-β type II receptor (Tgfbr2), in germline cells results in OA-like knee joints in mice at one month of age. However, other studies suggest that the increased expression of Tgf-β1 in mature knee joints causes early onset OA in animal models. Interestingly, a human genetic study reports that a two-nucleotide deletion, 741-742del AT (nonsense mutation), in SMAD-3 causes early-onset OA in one family. This human genetic study also reports that a nucleotide change, 859C>T or 782C>T, in SMAD-3 increases the level of TGF-β1 and activity of the TGF-β1 signaling in two families associated with early-onset OA. The observation in these human families is consistent with the results from the animal models, indicating that the lack of Tgf-β1 signaling in the germline cell results in OA in developing joints and that increased Tgf-β1 signaling causes OA in mature joints. The plausible explanation for this "conflicting" role of TGF-β1 in the pathogenesis of OA is: effective TGF-β1 signaling acts in a dose-dependent manner or a developmental stage-dependent manner. The present study addresses the question as to whether inhibition of Tgf-β1 signaling prevents mature knee joints from being degenerated in mouse models of OA.

Method: 1) By use of conditional knock out techniques with aggrecan-CreERt2 mice and floxed Tgfbr2 mice, Tgfbr2 was removed from articular cartilage of knee joints in mice at two months of age. Mice without Tgfbr2 were kept for another 6 months or longer. Knee joints from the mice (n=4) and their corresponding control (n=4) were then collected for morphological analysis. 2) Type XI collagen-haploinsufficiency (Col11a1+/-) mice, a spontaneous mouse model of OA, were treated with a neutralizing TGF-β1 antibody (25 μg) by intra-articular injection into the knee joints at 2 months of age. An additional injection was performed 2 weeks after the first injection. Knee joints were collected from mice at 6 months (n=4) and control mice (n=4) after the second injection for morphological analysis. 3) Mice were subjected to destabilization of the medial meniscus (DMM) or sham surgery. Immediately following the surgery, the mice were treated with Losartan orally (0.6g/1L drinking water) for 4 weeks (other studies indicate that Losartan reduces the expression of Tgfbr2). The average intake of Losartan was about 2.5mg/10g mouse body weight/day. Mice without the treatment of Losartan served as controls. Mice were sacrificed at 8 weeks (n=6) following the surgery for collection of knee joints. 4) Mice without Tgfbr2 at two months of age were subjected to DMM to induce articular